US005716642A

# United States Patent [19]

Bagchi et al.

[11] Patent Number: 5,716,642

[45] Date of Patent: Feb. 10, 1998

[54] **MICROPRECIPITATION OF NANOPARTICULATE PHARMACEUTICAL AGENTS USING SURFACE ACTIVE MATERIAL DERIVED FROM SIMILAR PHARMACEUTICAL AGENTS**

[75] Inventors: **Pranab Bagchi**, Webster, N.Y.; **Gregory L. McIntire**, West Chester, Pa.; **John R. Minter**, Rochester, N.Y.

[73] Assignee: **Nano Systems L.L.C.**, Collegeville, Pa.

[21] Appl. No.: **370,928**

[22] Filed: **Jan. 10, 1995**

[51] **Int. Cl.**[6] ..... **A61K 9/14**

[52] **U.S. Cl.** ..... **424/489**; 424/490; 424/9.1; 424/9.4

[58] **Field of Search** ..... 424/489, 7.1, 404, 424/9

[56] **References Cited**

U.S. PATENT DOCUMENTS

| | | | |
|---|---|---|---|
| 4,107,288 | 8/1978 | Oppenheim et al. | 424/22 |
| 4,250,113 | 2/1981 | Nordal et al. | 564/153 |
| 4,310,507 | 1/1982 | Luckey | 424/4 |
| 4,396,598 | 8/1983 | Lin | 424/5 |
| 4,489,055 | 12/1984 | Couvreur et al. | 424/7.1 |
| 4,540,602 | 9/1985 | Motoyama et al. | 427/213.31 |
| 4,713,249 | 12/1987 | Schroder | 424/488 |
| 4,725,442 | 2/1988 | Haynes | 424/490 |
| 4,826,689 | 5/1989 | Violanto et al. | 424/489 |
| 5,118,528 | 6/1992 | Fessi et al. | 427/213.36 |
| 5,145,684 | 9/1992 | Liversidge et al. | 424/489 |
| 5,260,478 | 11/1993 | Bacon et al. | 560/110 |
| 5,264,610 | 11/1993 | Bacon | 560/47 |
| 5,314,679 | 5/1994 | Lewis et al. | 424/9 |
| 5,318,767 | 6/1994 | Liversidge et al. | 424/4 |

OTHER PUBLICATIONS

Radiology, Jan. 1982, vol. 142, pp. 115–118.

Lachman, et al, "The Theory and Practice of Industrial Pharmacy", Chapter 2, Milling, p. 45, (1986).

Handbook of Experimental Pharmacology, vol. 73, pp. 56–73, 1984.

Investigative Radiology, vol. 29, Jul.–Aug. 1994.

International Journal of Pharmaceutics, 52(1989) 101–108.

*Primary Examiner*—Thurman K. Page
*Assistant Examiner*—William E. Benston, Jr.
*Attorney, Agent, or Firm*—Rudman & Balogh

[57] **ABSTRACT**

This invention describes the preparation of nanoparticulate pharmaceutical agent dispersion via a process that comprises the dissolution of the said pharmaceutical agent in an alkaline solution and then neutralizing the said solution with an acid in the presence of suitable surface-modifying, surface-active agents to form a fine particle dispersion of the said pharmaceutical agent. A combination of surface active surface modifying agents comprising a nonionic surface active substance and an anionic surface active material having a chemical structure which is at least on a molecular basis 75% similar to the pharmaceutical agent is used. This process is preferably followed by steps of diafiltration clean-up of the dispersion and then concentration of it to a desired level. This process of dispersion preparation leads to microcrystalline particles of Z-average diameters smaller than 400 nm as measured by photon correlation spectroscopy. Various modifications of precipitation schemes are described, many of which are suitable for large-scale manufacture of these agent dispersions.

**30 Claims, 9 Drawing Sheets**